the recited monoclonal antibody or fragment thereof specifically binds to the recited antigen. Support for this amendment may be found, for example, on page 18, lines 3-4, of the application. Claims 1-32 have been withdrawn by the Examiner from further consideration pursuant to 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention and the Examiner has made the restriction requirement final. The Examiner states that claims 1-32 will be subject to rejoinder at applicant's request once claims 40, 41 and 44-89 are directed to an allowable product. The Examiner further mentions that process claims which do not depend from or otherwise include all the limitations of an allowable product will not be rejoined.

Applicant makes of record herein that the response to the third restriction requirement (restriction requirement mailed October 9, 2001) submitted November 7, 2001 was fully responsive and that the Supplemental Response filed by applicant on February 14, 2002 was at the request of Examiner Rawlings, as noted in the Supplementary Response.

The oath or declaration is asserted to be defective, and various claims stand rejected under 35 U.S.C. § 112, first and/or second paragraphs, and under 35 U.S.C. § 103(a) over cited documents. Applicant will discuss each objection and rejection of record in the order presented in the Action. In view of this discussion, it is believed that each objection and rejection of record is overcome, and that the claims are in condition for allowance. Reconsideration of the application is respectfully requested.

Oath/Declaration

It is asserted that the oath/declaration is defective as a non-initialed and non-dated alteration has been made to the declaration. Applicant submits herewith a properly executed oath or declaration. Entry of the oath or declaration in the file and withdrawal of the objection to the oath or declaration are requested.

Rejections and objections under 35 U.S.C. § 112, first paragraph

The specification is objected to and claims 52 and 74 stand rejected under 35 U.S.C. § 112, first paragraph, as it is asserted that the specification fails to provide an

adequate written description of the invention and fails to provide an enabling disclosure because the specification fails to provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description; or (3) deposited. It is specifically asserted that it is unclear if a cell line that produces an antibody having the exact structural and chemical identity of the claimed humanized antibodies (N901 or C242) is known and publicly available or can be reproducibly isolated without undue experimentation. The rejection is hereby traversed, as such antibodies may be produced by the skilled artisan without undue experimentation by producing, for example, murine monoclonal antibodies and humanizing the antibodies, both by methods well known to the skilled artisan.

As mentioned on page 16, line 26 to page 17, line 1, of the application: "Particularly well known in the art are techniques for creating monoclonal antibodies produced by immunizing mice, rats, hamsters or any other mammal with the antigen of interest such as the intact target cell, antigens isolated from the target cell, whole virus, attenuated whole virus, and viral proteins such as viral coat proteins." For example, methods of producing C242 are known to the art and described, for example, in U.S. Patent No. 5,552,293 (submitted herewith as Exhibit A) as mentioned on page 18, lines 19-22, of the application. Methods of producing N901 are also known to the art, as evidenced by Griffin et al., *J. Immunol.*, 130(8):2947-2951 (1983) submitted herewith as Exhibit B. Notwithstanding this ability of the skilled artisan to produce such antibodies, a hybridoma cell line having use in the invention and producing a C242 antibody was deposited by an entity unrelated to the present inventor at the European Collection of Animal Cell Cultures (ECACC) in the United Kingdom under depository accession number 90012601 as noted in U.S. Patent No. 5,552,293 (Exhibit A).

Once murine hybridomas are obtained for the respective antibodies, the antibodies may be humanized by application of different humanization technologies known to the art and described, for example, in U.S. Patent Nos. 5,225,539 (Exhibit C); 5,585,089 (Exhibit D); and 5,639,641 (Exhibit E); as mentioned in the application on page 18, lines 25-28. Additionally, methods of producing different versions of humanized N901 have been specifically described in the scientific literature. See, for

example, Roguska *et al. Proc. Natl. Acad. Sci. USA*, 91:969-973 (1994) and Roguska *et al. Protein Eng.*, 9:895-904 (1996) mentioned on page 18, lines 28-30, of the application. Both of these references were previously submitted in an Information Disclosure Statement for the present application.

For example, humanized N901 has been produced by a "resurfacing" process described in Roguska *et al.*, *Proc. Natl. Acad. Sci*, 91:969-973 (1994). Briefly, in such a process, the complementarity-determining regions (CDRs) and the core of the murine variable region framework are maintained and the surface residues of the framework region are replaced with those from a human variable region. After obtaining, for example, the cDNA of N901 from a murine hybridoma and resurfacing N901 V_H and V_L genes as described on page 970, column 1, of Roguska *et al.* (1994), the cDNA encoding the resurfaced antibody can be transiently transfected into COS cells and the humanized antibody can be purified by staphylococcal protein A affinity chromatography as described in Roguska *et al.* (1994). Such a procedure may similarly be performed for C242 by the skilled artisan without undue experimentation. Therefore, the specification provides a written description that is more than sufficient to enable one skilled in the art to produce humanized versions of C242 and N901 and to thereby practice the invention defined by, for example, the rejected claims. Withdrawal of the rejection of claims 52 and 74 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 48-53, 56, 70-75 and 78 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. It is specifically asserted that claims 48, 49, 52, 70, 71 and 74, are indefinite in recitation of "fragment thereof". It is asserted in the Action that it can not be ascertained whether the claims require the fragment of the antibody to be able to bind the antigen to which the antibody binds and that one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

One skilled in the art would be aware that the fragment has the capability of binding to the antigen. Notwithstanding this, the specification also supports this

understanding. For example, on page 18, lines 13-18, it is taught that the monoclonal antibody or fragment thereof can be any other antibody that binds to the, for example, CD56 antigen with the same specificity as N901. It is clear from the specification that the fragment has the capability of binding to the antigen to which the antibody binds, and one skilled in the art would be aware of this fact.

Claims 50, 51, 72 and 73 stand rejected under 35 U.S.C. § 112, second paragraph, as it is asserted (1) the phrase "capable of binding" does not recite the condition under which the claims require the antibody or fragment thereof to be capable of binding the antigen expressed by a cancer cell or a CD56 antigen; (2) it is unclear whether the claims require the antibody or fragment thereof to actually be able to bind the antigen or merely have the potential to bind; and (3) it is not clear whether the claims require the antibody or fragment thereof to bind specifically or non-specifically.

Although applicant believes one skilled in the art would understand such a term, applicants have amended claims 50, 51, 72, and 73 in a sincere attempt to advance prosecution in this case. Applicant has amended the claims to indicate that the monoclonal antibody or fragment thereof specifically binds to the recited antigen.

It is further asserted that claims 52 and 74 are indefinite dues to the use of the designations "N901" and "C242" as the sole means of identifying the humanized antibodies to which the claims refer. It is further asserted that the use of laboratory designations only to identify a particular antibody renders the claims indefinite because different laboratories may use the laboratory designations to define completely distinct antibodies. Not only has the Action not provided evidence that other laboratories use these designations for completely different antibodies, one skilled in the art, especially in light of the specification which specifically references publications particularly describing the N901 or C242 antibodies (see, e.g., page 17, line 27 to page 18, line 2; and page 18, lines 19-22), is well-aware of the metes and bounds of the claims referring to N901 and C242.

Claims 52 and 74 further stand rejected under 35 U.S.C. § 112, second paragraph, as it is asserted that the limitation "wherein the monoclonal antibody or fragment thereof is humanized N901 or humanized C242" is indefinite as "humanized

N901 and humanized C242 antibodies are not fragments of antibodies, nor are they monoclonal antibodies in the strictest sense." Although applicant believes one skilled in the art would understand claims 52 and 74 as they are presently written, applicant has amended these claims in a sincere attempt to advance prosecution in this case. Specifically, applicant has amended claims 52 and 74 to indicate that the monoclonal antibody is humanized N901 or C242 and the fragment of the monoclonal antibody is a fragment of humanized N901 or humanized C242.

Claims 53 and 75 stand rejected as it is asserted that the limitation "wherein the monoclonal antibody or fragment thereof is Fv, Fab, Fab' or F(ab')2" is indefinite as "a monoclonal antibody is not a Fv, Fab, Fab' or $F(ab')_2$". Although applicant believes one skilled in the art would understand claims 53 and 75 as they are presently written, applicant has amended these claims in a sincere attempt to advance prosecution in this case. Applicant has specifically amended claims 53 and 75 to indicate that the fragment of the monoclonal antibody is Fv, Fab, Fab' or $F(ab')_2$.

Claims 56 and 78 stand rejected as it is asserted the term "a taxane mechanism" is indefinite as "it is unclear by which mechanism the claims require the compound to act; it is also unclear how and upon what subject matter, the claims require the compound to act."

As known in the art and as described, for example, on page 23, line 26 to page 24, line 2, of the application, "Taxane compounds prevent the growth of cancer cells by affecting cell structures called microtubules...Taxane compounds stop the microtubules from breaking down, such that the cancer cells become clogged with microtubules so that they cannot grow and divide." Additionally, it is seen on page 25, lines 12-16, that "Compounds that act through a taxane mechanism include compounds that have the ability to exert microtubule-stabilizing effects and cytotoxic activity against rapidly proliferating cells...." Examples of such compounds are provided, for example, on page 25, lines 16-26 of the application. As it is clear to the skilled artisan of the mechanism by which taxane compounds work, and several examples of such compounds are provided in the application and one skilled in the art would be familiar with these and other such compounds, the claims are definite to the skilled artisan. Withdrawal of the

rejection of claims 48-53, 56, 70-75 and 78 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 40, 41 and 44-89 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Liu et al. [*Proc. Natl. Acad. Sci. USA* 93:8618-8623 (1996)] in view of Mendelsohn [*Clinical Cancer Res.* 3:2703-2707 (1997)] and Hortobagyl [*Oncology* 11:11-15 (1997)].

Liu *et al.* is relied on for teaching an immunotoxin comprising a humanized antibody (C242) that is conjugated to a maytansinoid and also for teaching "a chemotherapeutic agent, namely 5-fluorouracil (5-FU)". It is admitted in the Action that Liu *et al.* do not teach a kit and do not teach a composition of an immunoconjugate and a chemotherapeutic agent.

Mendelsohn is relied on for teaching that combining a therapeutic chimeric antibody with a chemotherapeutic drug successfully eradicates well-established tumor xenografts that resist treatment with either agent alone.

Hortobagyl is relied on for teaching (1) a rationale for combination therapy; (2) many different chemotherapeutic agents, including paclitaxel, vinorelbine, etoposide, cisplatin and doxorubicin and that combinations of docetaxel and other agents have been shown to be highly active in preclinical mode; and (3) that synergies, or at least additive effects, were observed in studies with two- and three-drug combinations.

It is concluded that it would have been *prima facie* obvious to one of ordinary skill in the art to manufacture a kit comprising at least one, if not several, chemotherapeutic agents currently in development and widely known in the art. It is asserted one skilled in the art would have been motivated to manufacture such a kit because "the kit could be used to find effective combinations, strategies and regimens, and to determine optimal roles for one agents [sic] in relation to the others". It is further concluded that it would have been *prima facie* obvious to make a composition comprising one or the other immunoconjugates of Liu et al. and further comprising at least one of the chemotherapeutic agents currently under development and widely known in the art. It is

asserted that one of ordinary skill in the art would have been motivated to determine if a combination of the immunoconjugate of Liu, *et al.*, and one ore more of the chemotherapeutic agents "be [sic] more effective than any of the agents alone, since both Mendelsohn and Hortobagyl teach that combination therapy is often more effective than monotherapy because synergistic or additive effects are often observed in the former." This rejection is hereby traversed, as there is no teaching or suggestion of modifying Liu *et al.*, as suggested in the Action, because Liu *et al.* teach away from such a modification and applicant has observed unexpected efficacy of the claimed kits and compositions.

As the Examiner is aware, a conclusion of "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so." *ACS Hospital Sys. Inc., v. Montefiore Hospital et al.*, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984) (emphasis in original).

Liu *et al.* teach that the immunoconjugate C242-DM1 was "highly cytotoxic toward cultured colon cancer cells in an antigen-specific manner and showed remarkable anti-tumor efficacy *in vivo*." It was further found that injections of C242-DM1 in animals bearing COLO 205 tumors resulted in complete tumor regression lasting 5 weeks and no indication of toxic side effects as assessed by body weight loss was observed as recited on page 8622, column 1, of Liu *et al.* It is further mentioned in the same column that tumors treated with 5-FU grew rapidly to large sizes. Additionally, it is further mentioned in the Discussion section of the paper on page 8622, second column, that "5-FU, the standard chemotherapeutic drug used for the treatment of colorectal cancer, showed very little therapeutic benefit against the same tumors." After reviewing Liu *et al.*, at most, one skilled in the art would be motivated to utilize the immunoconjugate C242-DM1 alone, as it "showed remarkable anti-tumor efficacy *in vivo*", no indication of toxic side effects was observed and thus teaches away from combination therapy.

Mendelsohn discusses anticancer therapy utilizing doxorubicin or cisplatin in combination with a monoclonal antibody. Hortobagyl discusses treatment of breast cancer using docetaxel in combination with, for example, one or two drugs selected from cyclophosphamide, fluorouracil, vinrelbine, methotrexate or etoposide. There is no teaching or suggestion in either Mendelsohn or Hortobagyl of a kit or composition that includes at least one immunoconjugate, nor is there any teaching or suggestion of modifying Liu *et al.* to provide a kit or composition that includes at least one immunoconjugate and at least one chemotherapeutic agent as recited in the rejected claims. The assertion in the Action that one skilled in the art would have been motivated to manufacture a kit that includes "Docetaxel, Paclitaxel, Vinblastine, Navelbine, olastatin, cryptophycin, cisplatin, epothilone, Etoposide, Camptothecin and the C242-DM1 immunoconjugate of Liu, *et al.*" because "the kit could be used to find effective combinations, strategies, and regimens, and to determine the optimal roles for one agents [sic] in relation to the others" is no more than an improper obvious to try rationale. Any such teaching or suggestion can only come from impermissible hindsight analysis using the applicant's disclosure as a guide. Additionally, there is not teaching or suggestion in Liu *et al.*, Mendelsohn or Hortobagyl, either alone or combined, of the unexpected efficacy of the claimed kits and compositions.

As the Examiner is aware, secondary considerations must be taken into account in making a determination of obviousness. See *Stratoflex, Inc. v. Aeroquip Corp.*, 218 U.S.P.Q. 871 (Fed. Cir. 1983). For example, unexpected results are evidence of non-obviousness. See *In re Corkill*, 226 U.S.P.Q. 1005, 1009 (Fed. Cir. 1985) ("A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness...of the claims at issue").

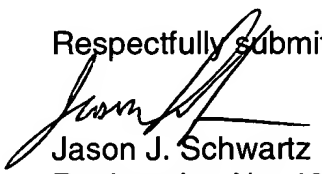
In the present case, it has unexpectedly been discovered that recited compositions of immunoconjugates and chemotherapeutic agents delay tumor growth longer than one would expect for an additive anti-tumor effect of the individual components. For example, in Example 3 of the application, it has unexpectedly been discovered that a tumor growth delay of twelve days was observed when SCID mice with tumors derived from NCI N417 cells were treated with huN901-DM1 in combination

with cisplatin and etoposide, whereas a tumor growth delay of four days was obtained in animals treated with either huN901-DM1 or cisplatin and etoposide. The tumor growth delay of 12 days is thus 50% longer than the eight days one would expect for an additive anti-tumor effect of the individual treatments.

As a further example, as seen in Example 4 of the application, in a similar experiment involving treatment with docetaxel alone, huN901-DM1 alone or a combination of docetaxel and huN901-DM1, treatment with docetaxel or huN901-DM1 alone resulted in tumor growth delays of 8 days and 20 days, respectively. In contrast, treatment with the combination of docetaxel and huN901-DM1 resulted in complete tumor regression in all the treated animals. The tumor was eradicated in 3 out of 6 animals in this treatment group, resulting in cures lasting greater than 200 days. In the remaining 3 animals in this group, there was a tumor growth delay of 52 days, which is 24 days longer than the calculated additive effect of the treatment with docetaxel and huN901-DM1 alone. Other such unexpected, synergistic and otherwise surprising results are found in Examples 2, 5, 6 and 7 of the application. Such superior, unexpected, synergistic and otherwise surprising results are not taught or suggested in Liu *et al.*, Mendelsohn, or Hortobagyl, either alone or combined. Withdrawal of the rejection of claims 40, 41 and 44-89 under 35 U.S.C. § 103(a) is respectfully requested.

In light of the foregoing, it is believed that all objections and rejections of records have been obviated and that the claims are in condition for allowance. Action towards this end is respectfully requested. The Examiner is invited to telephone the undersigned attorney to discuss any matters that may be handled in that fashion.

Respectfully submitted,



Jason J. Schwartz
Registration No. 43,910

Date: August 23, 2002
Hale and Dorr LLP
1455 Pennsylvania Avenue, NW
Washington, DC 20004
Phone: 202-942-8400